OCULAR TREATMENT USING CYCLOSPORIN-A DERIVATIVES

[0001] The present invention generally relates to treatment of ocular diseases and disorders and more specifically relates to a method for treatment of aqueous deficient dry-eye state, phacoanaphylaxis endophthalmitis and uveitis using certain cyclosporin derivatives.

[0002] The exposed part of a normal eye is covered by a thin tear film. The presence of a continuous tear film is important for the well-being of the corneal and conjunctival epithelium and provides the cornea with an optically high quality surface. In addition, the aqueous part of the tear film acts as a lubricant to the eyelids during blinking of the lids. Furthermore, certain enzymes contained in the tear fluid, for example immunoglobin A, lysozyme and beta lysin, are known to have bacteriostatic properties.

[0003] A sound lacrimal system functions to form and maintain a properly structured, continuous tear film. The lacrimal apparatus consists of the secretory system (the source), the distribution system, and the excretory system (the sink). In the secretory system, aqueous tears are supplied by main and accessory lacrimal glands.

[0004] The bulk of the tear film is made of such aqueous tear. The continuous production and drainage of aqueous tear is important in maintaining the corneal and conjunctival epithelium in a moist state, in providing nutrients for epithelial respiration, in supplying bacteriostatic agents and in cleaning the ocular surface by the flushing action of tear movement.

[0005] Abnormalities of the tear film include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS).

[0006] In relatively mild cases, the main symptom of KCS is a foreign body sensation or a mild scratchiness. This can progress to become a constant, intense burning or irritative sensation that can be debilitating to a patient.

[0007] More severe forms can progress to the development of filamentary keratisis, a painful condition characterized by the appearance of numerous strands or filaments attached to the corneal surface. Evidence suggests that these filaments represent breaks in the continuity of normal corneal epithelial cells. The shear created by lid motion pulls these filaments, causing pain. Management of this stage of KCS is very difficult.

[0008] A frequent complication of KCS is secondary infection. Several breakdowns in the eye's normal defense mechanisms seem to occur, presumably attributable to a decrease in the concentration of antibacterial lysozyme in the aqueous tears of a patient suffering from KCS.

[0009] Although KCS can develop in the absence of any other overt system abnormality, there is a frequent association of KCS with systemic disease. KCS can occur as part of a larger systemic involvement known as Sjogren's syndrome. This classically consists of dry eyes, dry mouth and arthritis.

[0010] Histologically, in KCS (as part of Sjogren's syndrome or in isolation), the initial changes seen in the lacrimal glands are those of focal lymphocytic and plasma cell infiltrates associated with degeneration of glandular tissue. These changes resemble those seen in autoimmune disease in other tissue, giving rise to the speculation that KCS has an autoimmune basis.

[0011] Sjogren's syndrome is recognized as an exocrine gland dysfunction. Characteristically, the lacrimal glands show a mononuclear cell infiltration that ultimately leads to destruction of the glandular structure.

[0012] Conventional treatment of KCS is symptomatic. Normally, aqueous-deficient dry eye states are treated by supplementation of the tears with artificial tear substitutes. However, relief is limited by the retention time of the administered artificial tear solution in the eye. Typically, the effect of an artificial tear solution administered to the eye dissipates within about thirty to forty-five minutes. Thus, the effect of such products, while soothing initially, does not last long enough. The patient is inconvenienced by the necessity of repeated administration of artificial tear solution in the eye as needed to supplement the normal tears. Moreover, such treatment merely acts to alleviate the symptoms of the dry eye state and does not cure any underlying disorders or causes of the dry eye state.

[0013] Histologic studies of the lacrimal glands in patients suffering from Sjogren's syndrome have shown some evidence of lacrimal gland inflammation. Such inflammation may be simply due to the normal aging of the patient. It has been suggested that the use of anti-inflammatory agents might serve to decrease the glandular inflammation. The systemic use of corticosteroids has been advocated in these conditions. However, the merit of systemic corticosteroids in dry eye states has not been established. In most dry eye cases, the hazards of long term use of anti-inflammatory agents would seem to outweigh their potential merit.

[0014] Surgical procedures have also been suggested in the management of dry eye states. Where there has been significant conjunctival destruction, mucous membrane transplants have been advocated. It has also been suggested that parotid (saliva) duct transplantation can be useful in the management of dry eyes. However, surgical alterations to combat dry eye conditions constitute a dramatic remedy and any benefit resulting from these alterations is questionable.

[0015] It has also been suggested to administer orally a dilute solution of pilocarpine to stimulate the autonomic nervous system to effect increased aqueous tear production. This method of treatment has not met with universal favor because of many unpleasant side effects of ingested pilocarpine.

[0016] Animal models of Sjogren's syndrome have been instrumental in basic ophthalmic research. A Sjogren's-like disease has been found in dogs with systemic luperythematosus. This disease, which may be referred to as canine KCS, is a common, chronic, progressive, and potentially blinding disease. A continuum of corneal and conjunctival lesions